REMARKS

The official action of 9 December 2008 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Independent claims 115 and 141 have been amended in accordance with the description in the specification as filed at, for example, paragraphs [0011], [0026], [0036] and [0064]. Specifically, paragraph [0036] describes the dosage that is released by irradiation of a selected element and paragraph [0064] identifies the iodine in the rose bengal as the selected element that is irradiated to cause the emission of Auger electrons in the described dose. See, also, original claims 118-120.

Claims 115, 122 and 124-147 stand rejected under 35 USC 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The basis for the rejection appears to be that the specification allegedly does not show that, as of the application filing date, Applicants had possession of the invention now being claimed insofar as the specification as filed allegedly does not describe that: (1) rose bengal accumulates in the lysosomes, or (2) the recited x-rays are directed to the lysosomes. See Official Action at page 3. The Examiner also states that the prior amendment changed the scope of the claims, but this is of course permissible so long as the change is expressly, implicitly or inherently described in the originally filed disclosure. See MPEP 2163.05.

In the present case, the originally filed disclosure describes each of (1) and (2) above. Specifically, the specification as filed describes that the rose bengal accumulates in the lysosomes. See specification at, e.g., paragraph [0063] ("Rose bengal accumulates in the cytoplasm of cells, particularly in lysosomes."). The specification as filed also describes that x-rays are directed to the rose bengal that accumulates in the lysosomes. See specification at, e.g., paragraph [0063]:

> "Lysosomes contain a number of hydrolytic enzymes capable of breaking down proteins and certain carbohydrates. Shining light on such cells leads to significant oxidative damage which leads to disruption of the lysosomes and cell death. With four iodine atoms per molecule of rose bengal, the use of line emission x-rays tuned to iodine (i.e. from a lanthanum target end window transmission x-ray tube (as described herein) will lead to a massive Auger cascade and disruption of the lysosomes and cell death."

The specification as filed thus shows that Applicants had possession as of the application filing date of the invention defined by the claims as amended. This being the case, Applicants have complied with the written description requirement. See MPEP 2163.02. Accordingly, Applicants respectfully submit that the rejection should be withdrawn.

Claims 115, 122, and 124-147 stand rejected under 35 USC 103(a) as allegedly being unpatentable over Cash et al in view of Wang and Ariel et al. Applicants respectfully traverse this rejection.

The claimed invention is based at least in part upon Applicants' discovery that, with the use of bright x-ray beams of defined line emissions tuned to the absorption edge of a selected element (iodine) in rose bengal, it is possible to cause the emission of Auger electrons from rose bengal accumulated in the lysosomes of irradiated cells in a dose of at least 10^6 Gy within a few atomic distances from iodine in the rose bengal. This causes the disruption of the lysosomes and death of the cells containing such lysosomes (specification at paragraph [0063]), while localizing the damage to such cells (specification at paragraph [0065] and [0038]).

This is explained in greater detail in the Declaration under 35 USC 1.132 of Dr. C.G. Wang submitted herewith. As discussed in the declaration, rose bengal accumulates within the lysosomes of cells and the Auger electrons from an Auger cascade caused by irradiating the cells with line emission x-rays tuned to the K-absorption edge of iodine deliver 10^6 Gray in a very small ionization sphere. This sphere of damage is so localized (a few atomic distances) that it would be harmless everywhere in a cell except the DNA and the lysosomes in the cell. Thus, the Auger cascade can be used to destroy the cells by flooding the cytoplasm of the cells with HCl from the lysosomes without destroying other cells outside of the very small ionization sphere.

In contrast, the primary reference, Cash et al, teaches the use of heavy elements as X-ray intensifiers but does not show or suggest the use of line emission x-rays to cause emission of Auger electrons from the iodine in rose bengal accumulated in the lysosomes of cells in a dose of at least 10^6 Gy within a few atomic distances from iodine in the rose bengal whereby to cause disruption of the lysosomes and death of the irradiated cells without destroying surrounding cells. In fact, insofar as Cash et al teach the necessity of limiting the dose of radiation used in the method described therein, they teach away from a method which generates a dose of at least 10^6 Gy. See Cash et al at, e.g., column 12, lines 43-48 ("a preferred approach is to irradiate the patient 10 so that the tumor receives 1600 cGy in a single dose, and the surrounding healthy tissue receives 1600/de cGy."); see, also, column 15, Example 1 ("At the skin, a dose of 10 Gy accumulates, which is too high for healthy skin.").

There is nothing in the reference which shows or suggests that the generation of Auger electrons of at least 10^6 Gy, as required in the claimed method, would be localized so as to prevent damage to normal tissue outside of a tumor to which irradiation is applied. In the absence of such teaching, the reference could not provide even a reasonable expectation of success with the claimed method.

The secondary references cited by the Examiner cannot supplement the deficiencies in the primary reference. In particular, Wang do not show or suggest

the use of line emission x-rays tuned to the K- or L- absorption edge of rose bengal to create an Auger cascade that can be used selectively to destroy tumor cells **without destroying healthy tissue**. Moreover, the primary reference teaches away from the need to tune x-rays to the K-edge of iodine. See Cash et al at column 6, lines 63-67 ("Iodine (I, element 53), a common element in contrast media, has its K-edge at 33.2 keV. At this low energy, x-rays penetrate only s short distance into the body, so x-ray sources are mostly configured to operate at energies above 34 keV, and there is no issue of tuning to the element."); see, also, Cash et al at column 9, lines 33-39. Finally, none of the cited references teaches that rose bengal accumulates in the lysosomes of cells such that the irradiation of iodine in the rose bengal can be used to turn the lysosomes in a cell into a therapeutic apparatus.

In view of the above, Applicants respectfully submit that the prior art rejection and all other rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Chia-Gee **WANG**, et al
Serial No.. 10/651,307 Group No. 1614
Filed: August 28, 2003 Examiner.. Alicia R. Hughes
For: CHEMOTHERAPY METHOD USING X-RAYS

Attorney Docket No.. **U 014776-3**

Commissioner for Patents
P O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, C.G. Wang, declare and state as follows:

1 I am a co-inventor of the invention described and claimed in the above identified patent application ("the application"). I make this declaration in support of the application to explain the difference between X-ray intensifiers, as described in the primary reference (Cash et al US Patent 6,366,801) cited by the Examiner in the prosecution of the application, and the claimed invention A copy of my curriculum vitae is attached to show my background and technical expertise.

2. X-ray intensifiers are generally the heavy elements with large scattering cross sections with X-ray photons. Barium, for example, is often used as the intensifying element to be embeded in a plastic sheet to function as the intensifying screen for X-ray images formed with visible fluorescent lighting. Similarly heavy elements such as Iodine can be used *in vivo* as intensifiers to increase the tissue cross section in intercepting the ionizing X-ray or γ-ray photon beam for radiation therapies. Not all intensifiers, however, are the same and serve the same function and purpose and can be applied in the same form and manner More specifically, the *in vivo* ionizing beam of radiation has an ionization range. γ-rays, for example, have a range typically measured in meters

(in water), and in order to deliver the dose exclusively on a particular physical location or specific to an organ/tissue, several γ-ray beams may be used to aim through this targeted location, each from a different angle, in order to deliver the desired integrated dose to the target while reducing the dose outside the targeted location to a minimum. For radioactive seeds implanted in the tissue, such as those for the prostate, the ionization range is typically selected for a few or few tens of cellular dimensions in order to deliver the maximum localized effect.

3. For intra-cellular radiation therapy, the ionization range must be selected to reach, but not much exceed, the selected organelles. The Auger electrons from an Auger cascade, for example, at 12-18eV each, would only reach 5-10 atomic dimensions in water and would deliver 10^6 Gray in a very small ionization sphere. This sphere of damage is so localized that it will be harmless everywhere in a cell except the DNA and the extremely small lysosomes that are composed of HCl acid Iodine element in an ionic form, would not typically enter a cell and then its lysosome. But Rose Bengal (Food Color Red #95), would typically enter the cell, any cell, particularly the tumor cells with more leaky plasma membranes. Once entered, the Rose Bengal would be digested by the lysosomes, again as a routine harmless cellular process. But upon shining an X-ray beam comprising line emission x-rays targeted energetically at the K-absorption edge of Iodine, the Auger dose from each of the 4 iodine atoms per molecule, which can be initiated repeatedly, could burst most of the lysosomes, flood the cytoplasm with HCl and kill the cell. That is, the harmless Rose Bengal under a specially designed X-ray beam becomes a therapeutic agent, just like a chemo-agent, except it has a localized effectiveness under the control of an X-ray beam.

4 I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such

willful false statements may jeopardize the validity or the application of any patent issued thereon.

April 9, 89
DATE

C.G WANG

Chia-Gee Wang (Principal Investigator, Nano)

Education/Training

University of Chicago		1958-63	Physics
Cornell University	Ph.D.	1963-68	Physics, Solid State

Research and Professional Experience

1958-63	While a student at the U. of Chicago, Dr. Wang was also a full time technical staff member at the Lab. for space and astrophysics building the first generation American scientific satellites. He developed the Si(Li) detector for X-ray spectroscopy. He was a graduate student of S. Chandrasekhar at the U.of Chicago
1963-67	While at Cornell University as a graduate assistant, Dr. Wang made extensive use of computer hardware for experimental data processing.
1967-67	As a post-doctoral fellow, Dr. Wang solved the Bethe-Goldstone equation on nuclear matters under Hans Bethe of Cornell U.
1967-72	Dr. Wang was a faculty member of the Physics Dept. of MIT, and taught most courses offered by the department. His specialty was astrophysics.
1972-75	Dr. Wang joined IBM research to do experimental solid state research.
Past 33 years	Dr. Wang has been an inventor-entrepreneur. He was a general partner of Wang Associates, an R & D partnership organized by Dr. A. B. Kinzel, a founding president of the Salk Institute. Dr. Wang founded Profile Diagnostics Sciences in 1986 to do molecular biology and NanoDynamics, Inc. in 1988 to do material science and device physics, including X-ray instruments. NanoDynamics has R&D contracts from the federal gov't. and product related contracts from major commercial companies.

Recent Publications

CG Wang, US Patent 7,430,276, Low dose x-ray mammography method; 2008

CG Wang, US Patent 7,180,981B2, High Quantum Energy Efficiency X-ray Tube and Targets; 2007

CG Wang and R TSU, US Patent 7,023,010. Si/C Superlattice useful for Semiconductor devices; 2006

CG Wang, US Patent 5,627,871; X-Ray Tube and Microelectronic Alignment Process; 1997

CG Wang, US Patent 5,044,001; Method and Apparatus for Investigating Materials with X-rays; 1991

CG Wang and Angus Hepburn, US Patent 5,861,244; 1/19/99. Genetic Sequence Assay using DNA Triple Strand Assay. (The subject matter got a Nobel Prize in Medicine in 2006)

CG Wang, R Tsu, J Lofgren, US Patent 6,376,337 B1; 4/23/02.Epitaxial SiO_x Barrier/Insulation Layer

R. Tsu, A. Filios, C. Lofgren, K. Dovidenko and CG Wang, Evidence of Silicon Epitaxy Beyond an Absorbed Monolayer of Oxygen", Electrochemical and Solid State Letters, 1, 80; 1998.

R. Tsu, A. Filios, C. Lofgren, C. Cahill, J. Vannostrand, and CG Wang, "An Epitaxial Si/O Superlattice Barrier", Solid State Electronics, 40, 221; 1996.